Claims 10-20, 26-33 and 37 have been canceled without prejudice as being drawn to non-elected inventions. Applicants reserve the right to pursue the canceled claims in one or more related applications.

Claims 1, 2, 8, 9, 21-24 and 36 have been amended and new claims 38-68 have been added to more particularly point out and distinctly claim that which Applicants regard as the invention. The amendments are fully supported by the specification. Support for the recitation of "as determined by the use of the BLASTp computer program" in claim 8 can be found at page 31, lines 11-21 and at page 46, line 6 through page 50, line 5. Support for the recitation of "cell surface" in claims 9, 22-24 and 36 can be found at page 11, lines 5-6. Support for new claims 38, 39, and 64 can be found in the specification at page 42, lines 9-12. Support for new claim 40 can be found in the specification at page 24, lines 28-31. Support for new claim 41 can be found in the specification, *inter alia*, at page 25, line 32 through page 26, line12. Support for new claim 42 can be found in the specification at page 26, lines 16-29. Support for new claim 43 can be found in the specification at page 26, lines 12-15. Support for new claim 44 can be found in the specification, *inter alia*, at page 29, lines 24-27, at page 30, lines 30-33 and at page 31, lines 11-21. Support for new claim 45 can be found in the specification, *inter alia*, at page 6, lines 5-8, at page 25, lines 25-26; at page 29, lines 24-27, and at page 30 at lines 33-36. Support for new claim 46 can be found in the specification, *inter alia*, at page 14, lines 20-21, at page 25, lines 25-26, and at page 30 at lines 33-36. Support for new claims 47-54 can be found in the specification, *inter alia*, at page 13, lines 6-7. Support for new claims 55 and 56 can be found in the specification, *inter alia*, at page 24, lines 28-32. Support for new claims 57-63 and 65-68 can be found in the specification, *inter alia*, at page 7, lines 23-25 and page 8, lines 3-5. No new matter is added.

The specification on page 25 has been amended to correct an obvious editorial error. In particular, two instances of references to "CDR 8, 9 [and/]or 10" have been corrected to recite "CDR 1, 2 [and/]or 3 (corresponding to SEQ ID NO:8, 9, [and/]or 10, respectively)." The recitation of CDR 8, 9 [and/]or 10 is clearly in error, as each antibody chain comprises only three CDRs. Additionally, the sentences in which the erroneous recitations are found refer to molecules and proteins comprising portions of the S2C6 heavy chain. Given that SEQ ID NOS:8, 9 and 10 correspond to the S2C6 heavy chain CDRs 1, 2 and 3, respectively, the context of the errors makes it clear that the intended references were to CDR 1, 2 [and/]or 3, or alternatively to SEQ ID NOS:8, 9 [and/]or 10.

The specification has also been amended at page ii of the Table of Contents and at page 58, to replace "DEPOSIT OF MICROORGANISM" with "DEPOSIT OF HYBRIDOMA." Support for the amendments can be found in the specification, *inter alia* at page 58, lines 23-25. Accordingly, the amendments to the specification introduce no new matter.

INTERVIEW SUMMARY RECORD

Applicants and Applicants' representatives thank Examiner Karen Canella for the courtesy of the recent interview in connection with the above-identified application. Pursuant to 37 C.F.R. § 1.133 and M.P.E.P. 713.04, Applicants presents this interview Summary Record of the interview of March 21, 2001 ("the Interview") between Examiner Karen Canella, Applicants Dr. H. Perry Fell and Dr. Joseph A. Francisco, and Applicants' representatives, Adriane M. Antler and Muna Abu-Shaar, in connection with the above-referenced application. During the Interview, the instant application was discussed.

The objection to the specification was discussed, Applicants' representatives noting that the specification would be amended as suggested. The claim rejections in the instant Office Action under 35 U.S.C. § 112, second paragraph, were discussed. In particular, the interview participants discussed claim amendments that would more particularly point out and distinctly claim the instant invention. Dr. Antler explained to the Examiner that the claim language "comprises one or more insertions or substitutions relative to native monoclonal antibody S2C6" ensures that the claims do not read on native S2C6. The rejections under 35 U.S.C. § 112, first paragraph for lack of enablement were also discussed. Applicants and Applicants' representatives presented reasons as to why the claimed invention was enabled, with particular reference to the availability in the art of straightforward methods for making and determining suitable amino acid substitutions in making antibody variants, including the use of structural modeling-based methods and phage display technology to identify antibody variants that retain functional activity of the parent antibody. The Examiner agreed to consider Applicants' arguments and invited Applicants to present additional data regarding any antibody variants actually made, by way of a Declaration under 37 C.F.R. § 1.132. Dr. Antler then presented reasons why, in view of the current written description guidelines and the prevailing case law, the specification provides a written description for the claimed invention. Finally, Applicants and Applicants' representatives discussed why the instantly claimed invention was not anticipated or made obvious by the prior art relied upon by the Examiner in the instant

Office Action, by pointing out the functional and/or structural differences between the claimed anti-CD40 antibodies and antibody derivatives and the prior art anti-CD40 antibodies. Accordingly, Examiner Canella agreed that the claims were not anticipated or made obvious by the prior art of record.

Further details of the arguments presented in support of patentability are found hereinbelow.

THE INVENTION

The present inventors have (i) cloned the gene sequences of the anti-CD40 antibody S2C6, (2) identified a novel activity for the antibody, that being increasing the binding of CD40 ligand to CD40 present on the cell surface, and (3) discovered anti-tumor properties associated with the antibody. The claims, as amended, of the instant application are directed to variants and derivatives of the antibody having one or more of the same complementarity-determining regions (CDRs) as the heavy chain of S2C6, or molecules that compete for binding to CD40 with S2C6 and have the ability to increase the binding of CD40 ligand to CD40 by at least 45%. Also encompassed by the invention are claims directed to pharmaceutical compositions comprising such variants and derivatives.

THE OBJECTION TO THE SPECIFICATION SHOULD BE WITHDRAWN

The Examiner objects to the specification on the grounds that it states, at page ii, line 19 and at page 58, line 21, "DEPOSIT OF MICROORGANISM" in reference to the deposit of the S2C6-producing hybridoma. Applicants have amended the specification to state "DEPOSIT OF HYBRIDOMA" and thus request that the objection be withdrawn.

DRAWINGS

Applicants note the objection to the drawings for the reasons set forth in form PTO-948. Applicants respectfully request that the objection be held in abeyance until receipt of a Notice of Allowability, at which point appropriate formal drawings will be submitted.

THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 1-9, 21-25, 34 and 36 have been rejected under 35 U.S.C. § 112, second paragraph, allegedly as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Specifically, claims 1, 8, 21, 23 and 36 are allegedly indefinite for the recitation of "immunospecifically binds CD40." The Examiner states that it is unclear how "immunospecifically" differs from "specifically." In order to expedite prosecution, Applicants have amended claims 1, 8, 21, 23 and 36 by deleting the term "immunospecifically."

The Examiner further states that "CD40" could refer to the CD40 antigen on B cells, soluble CD40 protein, or the CD40 ligand on T cells. Applicants respectfully note that the specification makes clear from the outset the distinction between CD40 and CD40 ligand ("CD40L") (*see, e.g.*, page 1, lines 15-20). Thus, CD40, as used by applicants, does not refer to CD40L. The ability of the antibodies of the invention to bind to CD40 on the surface of neoplastic cells and in the presence of CD40L costimulate CD40 signaling does not, however, preclude them from binding to soluble CD40. Unless otherwise indicated, CD40 recited in the claims can be cell surface CD40 or soluble CD40. Applicants have amended the claims, however, to state "cell surface CD40" in the context of the claim recitation relating to the ability of the antibody to enhance binding of CD40L to CD40 by at least 45%, as this more clearly defines the conditions under which such binding ability is measured.

Claim 8 is rejected under 35 U.S.C. § 112, second paragraph, because it references a percentage of sequence identity without reciting an algorithm by which the percentage identity is calculated. Claim 8 has been amended, and now states that the percentage of sequence identity is "as determined by use of the BLASTp computer program," thus obviating the rejection.

Claims 1, 6, 8, 9, 21, 22, 23 and 24 are rejected under 35 U.S.C. § 112, second paragraph, for failure to provides sufficient assurance that the conditions of 37 C.F.R. §§ 1.801-1.809 have been met with respect to the hybridoma deposited with the ATCC and assigned accession number PTA-110. In response to this rejection, Applicants submit concurrently herewith a "Statement of Attorneys for Applicants Regarding Permanence And Availability of Deposited Microorganisms" executed by attorney for

Applicants, Adriane M. Antler, which provides the requisite assurances, accompanied by a copy of the relevant International Form of deposit receipt from the ATCC.

In view of the foregoing, Applicants believe that all rejections under 35 U.S.C. § 112, second paragraph, have been obviated and respectfully request that the rejections be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF ENABLEMENT, SHOULD BE WITHDRAWN

Claims 9, 21-25 and 36 are rejected under 35 U.S.C. § 112, first paragraph, allegedly because the specification

> does not reasonably provide enablement for a protein comprising one or more substitutions or insertions in the primary amino acid sequence relative to that of the monoclonal antibody S2C6, or a protein that has at least 95% identity to SEQ ID NO:2 or SEQ ID NO:7 said protein having the ability to increase the binding of CD40 ligand to CD40 antigen by at least 45%.

The Examiner further argues that the specification does not provide "guidance for choosing which amino acids to exchange... and which amino acids can be substituted" in making variants of S2C6 that are not identical in the heavy and light chain regions.

Applicants respectfully assert that, for the reasons discussed below and according to the applicable case law, the instant specification does, indeed, fully enable one of skill in the art to make variants of S2C6, including variants that comprise insertions or substitutions in sequence relative to native S2C6, that retain the functional activity of the antibody, *i.e.*, the ability increase binding of CD40L to CD40 by at least 45% as recited by the rejected claims (such variants being hereinafter referred to as "functional variants" or "functional antibody variants").

THE LEGAL STANDARD

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988). In fact, well known subject matter is preferably omitted. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) ("a patent need not teach, and

preferably omits, what is well know in the art."). Further, one skilled in the art is presumed to use the information available to him in attempting to make or use the claimed invention. *See Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990) ("A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation."). These enablement rules preclude the need for the patent applicant to "set forth every minute detail regarding the invention." *Phillips Petroleum Co. v. United States Steel Corp.*, 673 F. Supp. 1278, 1291 (D. Del. 1991); *see also DeGeorge v. Bernier*, 768 F.2d 1318, 1323 (Fed. Cir. 1985).

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover,* 170 USPQ 276, 279 (CCPA 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands,* 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, so long as it is merely routine. *Id.*

Further, while the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of an experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue in *In re Angstadt,* 190 USPQ 214 (CCPA 1976):

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.

Id. at 219 (emphasis in the original).

THE INSTANT SPECIFICATION PROVIDES AMPLE GUIDANCE TO THE SKILLED ARTISAN FOR MAKING THE CLAIMED COMPOSITIONS

The instant specification, together with information which was readily available to the skilled artisan at the time the instant application was filed, provides a disclosure which fully enables the claimed invention.

With respect to the argument that the specification "does not reasonably provide enablement for a protein comprising one or more substitutions or insertions in the primary amino acid sequence relative to that of the monoclonal antibody S2C6" and further does not provide enablement for "a protein that has at least 95% identity to SEQ ID NO:2 or SEQ ID NO:7 said protein having the ability to increase the binding of CD40 ligand to CD40 antigen by at least 45%," Applicants note to the Examiner that the specification is rife with teachings of how to make and use the claimed molecules. Specifically, Applicants direct the Examiner's attention to Sections 5.6 (at pages 24-28) and 5.7 (at pages 28-35) of the instant specification. Sections 5.6 and 5.7 provide teachings on how to make monoclonal antibodies, humanized antibodies, chimeric antibodies, single chain antibodies, bispecific antibodies, Fab fragments, $F(ab')_2$ fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above (page 24, lines 28-32); antibody derivatives with substitutions, insertions or deletions relative to S2C6 (page 29, lines 24-27); fragments of S2C6 (page 30, lines 21-26); proteins with homology to S2C6 or that are encoded by a nucleic acid sequence that is capable of hybridizing under conditions of high stringency to S2C6-encoding sequences (page 20, lines 27-36); S2C6 fragments or derivatives that are differentially modified during or after translation (*e.g.*, by glycosylation) (page 32, line 32 to page 33, line 3); chimeric or fusion proteins comprising S2C6 or a fragment or derivative thereof and a second protein, such as a biological response modifier or a toxin (page 33, line 29 to page 34, line 16) or a chemotherapeutic agent (page 35, lines 20-27). Applicants have further supported their teachings by constructing, using conventional methods, a single chain anti-CD40 immunotoxin comprising the variable regions of S2C6 fused to the toxin bryodin 1 (BD1) (see Section 9 at pages 56-58 of the specification). The immunotoxin, referred to as BD1-S2C6 sFv, binds to CD40. Further, this binding is specific, as evidenced by the ability of excess native S2C6 to compete away the binding (see Figure 9).

As further evidence of the enabling nature of the disclosure, and in accordance with the Examiner's suggestion at the recent interview, Applicants submit herewith as Exhibit D a Declaration of Dr. Joseph A. Francisco under 37 C.F.R. § 1.132,

one of the inventors of the presently claimed invention ("the Declaration"). Dr. Francisco describes how, following guidelines for the construction of chimeric antibodies taught in the specification and using methods that are well known to the skilled artisan, a chimeric antibody was constructed comprising the S2C6 variable regions and human constant regions (*see* ¶ 6 of the Declaration). The antibody was tested for its ability to compete with S2C6 for binding to CD40 on Raji cells and was found to compete for S2C6 binding to Raji cells comparably to native S2C6 (*see* ¶ 7 of the Declaration). The chimeric antibody also exhibited anti-tumor activity *in vivo* against a murine xenograft model of human non-Hodgkin's lymphoma (*see* ¶ 8 of the Declaration). These data lead Dr. Francisco to conclude in ¶ 9 of the Declaration that "chimeric S2C6 has a binding affinity to CD40 that is similar to that of the parental monoclonal antibody S2C6, and is functionally equivalent to S2C6."

With respect to the Examiner's argument that the specification does not provide guidance for identifying amino acids that can be substituted for the amino acids of native S2C6, Applicants provide evidence that (i) to make functional variants of S2C6, it is not necessary to "design" specific amino acid alterations as methods for systematic yet random mutagenesis coupled with screening assays for functional variants were known in the art at the time the application was filed; and (ii) even in the absence of such methods in (i), well established methods were known in the art for choosing amino acids in an antibody's variable and framework regions that can be changed and the nature of the change, without destroying the utility (*i.e.*, binding specificity and affinity) of the antibody.

Phage Display-based Methods of Screening for Functional Antibody Variants

The Examiner states that Applicants have not enabled functional derivatives of S2C6, because of a lack of guidance in the specification as to which particular amino acid(s) can be altered to produce a functional derivative of S2C6. In response to this rejection, Applicants invite the Examiner to review the following Exhibits:

Exhibit E: Glaser *et al.*, 1992, J. Immunol.149:3903-13 ("Glaser");

Exhibit F: Yelton *et al.*, 1995, J. Immunol. 155:1994-2004 ("Yelton");

Exhibit G: Wu *et al.*, 1998, Proc. Natl. Acad. Sci. U.S.A. 95:6037-42 ("Wu");

Exhibit H: Barbas *et al.*, 1994, Proc. Natl. Acad. Sci. U.S.A. 91:3809-3813; ("Barbas"); and

Exhibit I: Schier *et al.*, 1996, J. Mol. Biol. 263:551-567 ("Schier").

These Exhibits are exemplary references that describe the use of phage display technology to increase the affinity of an antibody towards its antigen. The technology, referred to as affinity maturation, employs mutagenesis or CDR walking and re-selection on the antigen to identify antibody variants that bind with higher affinity to their antigen than the parental antibody.

Glaser describes a "codon-based" mutagenesis for "rapid and efficient modification of antibody" sequences expressed in Fab phage display systems (Abstract). Oligonucleotide mutagenesis using biased oligonucleotide pools that mutagenize entire codons rather than single nucleotides results in Fab phage display libraries with a semi-randomized repertoire of amino acid mutations (page 3904, right column). The libraries had a 67% lower incidence of stop codons than a library produced by total codon randomization, and the bias in the oligonucleotide pools used in library construction was such that at each amino acid residue in a given library, about 50% of the clones had the parental sequence (*Id.*). Glaser constructed two such libraries for the monoclonal antibody L6, one for light chain CDR1 alone and the other for both light chain CDR1 and CDR2 (page 3904, right column and page 3907, left column). The libraries were screened against an L6 anti-idiotypic antibodies and L6 variants with equal or improved affinity for the anti-idiotype were identified (*see, e.g.*, Tables V and VI, respectively).

The method disclosed in Glaser has been successful for the identification of high affinity variants of other antibodies, including BR96, an antibody recognizing Lewis Y-related antigens expressed on the surface of many human carcinomas. Like Glaser, Yelton employed codon-based mutagenesis to construct libraries of mutations of the heavy chain CDRs in an M13 phage Fab expression vector (page 1998, left column). Screening of the heavy chain CDR3 library identified a BR96 variant, M1, with 5- to 10-fold improved affinity to the BR96 antigen and tumor cell membranes (page 1998, left column). Screening of the heavy chain CDR2 library identified a BR96 variant, M2, with 4- to 5-fold improved affinity to tumor cell membranes (page 1999, left column). Combining the two variants resulted in a third variant, M3, of BR96 with a 30-fold improved affinity towards tumor cell membranes over native BR96 (page 1999, left column).

Wu describes the use of the Glaser method to construct libraries totaling less than 3,000 variants of Vitaxin, a humanized anti-integrin $\alpha_V\beta_3$ antibody. Each library consisted of a pool of variant clones, each of which clones differed from Vitaxin by a single amino acid alteration in a single CDR and contained variants representing each of the 19 possible amino acid substitutions for each CDR residue. A library was constructed for each

CDR, with the exception of CDR 2 of the heavy chain, which required the construction of two libraries (Wu at 6038, right column and 6039, left column). A primary round of screening by contacting immobilized variants with labeled integrin $\alpha_V\beta_3$ identified variant clones with greater than 3-fold increases in affinity to the antigen relative to Vitaxin (Wu at 6039, left column). Subsequent to this step, combinatorial libraries were made that combined the best light chain variants with the best heavy chain variants (Wu at 6039, right column) and the resulting clones subjected to ELISA to identify clones with improved affinity for $\alpha_V\beta_3$ (Wu at 6040, left column). Fourteen clones were identified in the second round of screening that displayed 18- to 92-fold higher affinities to $\alpha_V\beta_3$ than Vitaxin (Wu at 6040, left column). Wu describes the screening methods as "easy" and "rapid" (*see* page 6042, left column).

A related approach to that described by Wu was taken by Barbas. Barbas employed a CDR walking approach coupled with CDR screening to identify variants of the anti-gp120 antibody (gp120 being a surface glycoprotein of the human immunodeficiency virus, "HIV") HIV-4, with improved affinity to gp120 and a broader HIV strain cross reactivity than the native HIV-4. The first step in the approach taken by Barbas was to generate a fab phage display library of antibody variants in which the five residues of heavy chain CDR1 were randomized (Barbas at 3810, left column). Next, the variants underwent four rounds of affinity selection to identify those variants that best bound to gp120 (Barbas at 3810, left and right columns). In twelve clones of the clones identified, CDR3 of the heavy chain was randomized. These clones had four CDRs (heavy chain CDR2 and the light chain CDRs) that were identical to HIV-4, and two randomized CDRs (heavy chain CDR1 and 3). The resulting library of variants was subjected to affinity selection with gp120and four clones were identified for further analysis (Barbas at 3810, right column). These variants had similar neutralizing activity against the HIV strain (IIIB) from which the gp120 employed in the affinity maturation was derived to the parental HIV-4 antibody, and had improved neutralization activity against another HIV strain (MN) (Barbas, Table 1 at 3811). Thus, Barabas teaches that it is possible to generate antibody variants with one or two random CDRs and still be able to identify antibodies with functional characteristics that are similar to the parental antibody.

Again, the CDR walking method is not uniquely successful for Barbas. Another exemplary reference which uses CDR walking is Schier, which employed CDR walking in the context of scFv, rather than Fab, phage display. Schier subjected an scFv antibody that binds the tumor antigen c-erbB-2 (C6.5) to CDR walking, starting with partial

randomization of CDR3 of the light chain then selecting the highest affinity variant and proceeding to partially randomize CDR3 of the heavy chain (page 552, left column through page 553, right column and page 554). Schier successfully identified variants of C6.5 with a 1230-fold increase in affinity (page 559, left column).

Altogether, Exhibits E-I represent the well-founded knowledge in the art at the time of filing the present application that guided selection was not required to identify antibody variants with similar or enhanced affinities to their antigens relative to their parental counterparts.

Methods of Designing Functional Antibody Variants

The Examiner contends that, because the secondary and tertiary structures of proteins are often determined by interactions between amino acid residues, oftentimes one cannot introduce a substitution into a protein sequence without introducing a "compensatory" substitution to restore the shape and function of the original sequence. The Examiner concludes that, absent explicit teachings in the specification of particular amino acids to substitute, one of skill in the art would not know how to make or use the antibody variants of the present invention.

Applicants respectfully disagree with the Examiner's conclusion. One of ordinary skill in the art, by employing routine methods in a straightforward manner, can predictably obtain functional antibody variants in which one or more CDR and/or framework region amino acids have been changed relative to the parental molecule. As will become apparent by the discussion below, at the time of filing the present application, there were well established methods (i) for identifying antibody residues that can be altered without losing antibody binding specificity and affinity, (ii) for identifying residues that can be altered to enhance antibody affinity; and (iii) for determining how the residue should be altered (*i.e.*, which residue to introduce). These methods have been extensively employed to obtain functional antibody variants. Such methods are exemplified by the methods taught hereinbelow for making "compensatory" amino acid alterations in human framework regions onto which murine CDRs have been grafted.

One such method is described by Foote and Winter, 1992, J. Mol. Biol. 224:487-499 ("Foote"; attached hereto as Exhibit J). Foote describes an analysis of a number of variable domain structures to identify framework residues that affect the conformation of the CDRs. By inspection of several structures, Foote identified "framework residues forming a layer underlying the CDRs and that are positioned to ...

adjust CDR structure and fine-tune the fit to antigen." (Foote at page 497). These framework residues were termed Vernier residues and, for the V_H domains, these residues were determined to be residues 2, 27-30, 47-49, 67, 69, 71, 73, 78, 93-94, and 103 (Foote at page 497, Table 2). Foote indicates that, in order to preserve the activity of an antibody upon grafting donor CDR residues to acceptor CDR residues, amino acid change(s) are made in Vernier residues that are not conserved between the donor and recipient frameworks in order to obtain variable region packing and shape more similar to the CDR-donor antibody and thus with a similar affinity (Foote at page 497, right column).

An exemplary reference that demonstrates the utility of the teachings of Foote is Tempest *et al.*, 1995, "Identification of framework residues required to restore antigen binding during reshaping of a monoclonal antibody against the glycoprotein gB of human cytomegalovirus," Int. J. Biol. Macromol. 17:37-42 (attached hereto as Exhibit K; "Tempest"). Tempest describes the grafting of the CDRs from the murine antibody HCMV37, which binds to the gB envelope protein of human cytomegalovirus, onto human frameworks. Although the humanized antibody that resulted did not exhibit antigen binding, the substitution of Vernier V_H amino acids Thr28, Phe29, Ser30 with murine residues Ser28, Ile29, and Thr 30 restored significant binding. Tempest clearly states that the selection of residues Thr28, Phe29, Ser30 for alteration was based on teachings that were known in the art, including those of Foote. See Tempest, page 39, right column, which states that "[f]rom analysis of the crystal structure of Fabs, several interactions between FR [framework regions] and CDRs have been demonstrated, and the importance of some of these in antigen binding has been substantiated by protein engineering. Using these data, we examined V_H FR residues which may impinge on loop conformation and which differ between the murine and humanized heavy chains, " again citing to, *inter alia*, Foote. See also page 41, left column, for another example of the comparison of the murine framework sequence with the human framework sequence. "[R]esidues 28-30 appear to be somewhat species-specific; these are Ser-Ile-The (SIT) in HCMV37 and this motif is found in >95% of murine VH subgroup IA. In contrast, this tripeptide is not found in any reported human V region ...." Thus, this comparison, based on well established teachings, led to the changes in amino acids 28-30 which restored binding ability to the humanized antibody.

The Examiner is invited to examine the following additional references in which the principles set forth in Foote were used to obtain functional antibody variants: Tempest *et al.*, 1991, "Reshaping a human monoclonal antibody to inhibit human respiratory syncytial virus infection *in vivo*," Bio/Technology 9:266-271 (attached hereto as

Exhibit L); Tempest *et al.*, 1994, "Efficient generation of a reshaped human mAb specific for the toxin of Clostridium perfringens," Protein Eng. 7:1501-1507 (attached hereto as Exhibit M); Tempest *et al.*, 1994, "A humanized anti-tumor necrosis factor-α monoclonal antibody that acts as a partial, competitive antagonist of the template antibody," Hybridoma 13:183-190 (attached hereto as Exhibit N); and Graziano *et al.*, 1995, "Construction and characterization of a humanized anti-γ-immunoglobulin receptor type I (FcγRI) monoclonal antibody," J. Immunology 155(10):4996-5002 (attached hereto as Exhibit O).

Another method for selecting "compensatory" changes in human framework regions onto which murine CDRs are grafted is taught by U.S. Patent No. 5,585,089 to Queen ("Queen") (see also the related U.S. Patent Nos. 5,530,101; 5,693,761; 5,693,761; and 5,693,762). Queen, which issued on December 17, 1996, is referred to at page 26, lines 16-17 of the instant specification and is attached hereto as Exhibit P. Queen provides a set of guidelines, based on extensive computer modeling, that can be followed to preserve antibody activity when making CDR grafted antibody variants, for example humanized murine antibodies. These guidelines are set forth in the Summary of the Invention at Columns 2 and 3 and reference instances in which the human framework residue is changed into the corresponding murine residue:

> [1] the amino acid in the human framework region of the [human] acceptor immunoglobulin is rare for that position and the corresponding amino acid in the [murine] donor immunoglobulin is common for that position in human immunoglobulin sequences; or
>
> [2] the amino acid is immediately adjacent to one of the CDR's; or
>
> [3] the amino acid is predicted to be within about 3 [angstroms] of the CDR's in a three-dimensional immunoglobulin model and capable of interacting with the antigen or with the CDR's of the [murine] donor or humanized immunoglobulin.

Moreover, Queen teaches that if an amino acid residue in the human framework region is atypical for that position, as is its murine counterpart, the residue may be replaced with an amino acid typical for human sequences at that position. *Id.*

Following the above guidelines, Queen successfully designed humanized forms of six murine antibodies that had at least approximately equal affinity to their

antigens as their murine counterparts. One humanized form of a murine anti-Tac (or anti-CD25, the interleukin 2 receptor ligand) antibody comprising in the variable regions the sequence of the human antibody Eu with the exception of the CDRs, which were derived from the murine anti-Tac antibody, twelve murine V_H residues at positions 27, 30, 48, 67, 68, 93, 95, 98, 107-109, and 111 of the heavy chain, and three murine V_L residues at positions 48, 60 and 63 of the light chain (see column 38, lines 1-61). Like the parent anti-Tac antibody and with approximately the same affinity, this humanized anti-Tac antibody[2] bound to IL-2 receptor-expressing HUT-102 cells (see column 42, lines 23-57). See also column 44, line 61 through column 45, line 17, for a discussion of the binding affinities of the other antibodies humanized by the guidelines taught in Queen.

Additional methods for guided selection of to identify antibody variants are disclosed in U.S. Patent Nos. 5,766,886; 4,816,567; 5,714,350; and 5,565,332.

In view of the teachings of the specification and the teachings Applicants have shown to be well known in the art, Applicants respectfully assert that one of skill in the art at the time of filing the application would recognize how to make the changes in the framework regions and/or complementarity determining regions (CDRs) of S2C6 to produce functional variants of S2C6 without undue experimentation, and thus request that the rejection of claims 9, 21-25 and 36 under 35 U.S.C. § 112, first paragraph, for lack of enablement, be withdrawn.

If the Examiner is relying on any other facts within her personal knowledge as a basis for this rejection, she is hereby requested to supply an affidavit specifying with particularity the data supporting the rejection. 37 C.F.R. § 1.104(d)(2).

THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF WRITTEN DESCRIPTION, SHOULD BE WITHDRAWN

The Examiner has rejected claims 1-9, 21-25, 34 and 36 under 35 U.S.C. § 112, first paragraph, for lack of written description, stating that

> the written description in this case only set forth SEQ ID NO:1-10 therefore the written description is not commensurate in scope with the claims drawn to molecules comprising SEQ ID NO:3, 4, 8, 9 or 10 which comprise one or more substitutions or insertion[s] in the primary amino acid

[2] Referred to in column 42 as the "PDL humanized anti-Tac antibody" to distinguish it from the "CDR humanized anti-Tac antibody" which had all human framework residues.

sequence relative to the native monoclonal antibody S2C6 or a purified protein comprising an amino acid sequence having 95% identity to SEQ ID NO:2 or 7.

As indicated in the Office Action, a claimed genus must be supported by a description of relevant identifying characteristics of a representative number of species. *Regents of University of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied* 523 U.S. 1089 (1998). What constitutes a "representative number of species" depends upon the knowledge and skill in the art. *Eli Lilly*, 119 F.3d at 1568. The Examiner's reliance on *Fiers v. Revel*, 25 USPQ2d 1601 (Fed. Cir. 1993) and *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016 is misplaced.

The principle set forth in *Fiers* is that the description of a method of isolating a cDNA does not provide a written description of that cDNA. In *Fiers*, the Applicants' description of a method of isolating a human fibroblast β interferon DNA was asserted to have provided a written description of the DNA itself. The present situation is clearly distinguishable, as the instant specification teaches the sequence of heavy and light chain CDRs and variable regions of S2C6 and of a single-chain immunotoxin derivative thereof.

With respect to *Amgen*, the Federal Circuit concluded that one is not entitled to a claim of all analogs of a gene on the basis of disclosure of only one species. The present situation differs from that described in *Amgen*, *inter alia*, in that (i) a large number of species is described by Applicants in the specification and (ii) Applicants describe in the specification structural features common to the genus. The structural features common to the genus in claim 1 (and thus claims 2-7 and newly added claims 38-42 and 46-49) dependent thereon) is a heavy chain CDR (the heavy chain CDRs are SEQ ID NOS:8, 9, and 10) or variable domain (SEQ ID NO:7) (claim 2), which provides the appropriate specificity to the claimed molecules. With respect to claim 9, the recitation of "competes for binding to CD40 with monoclonal antibody S2C6 as secreted by the hybridoma deposited with the ATCC and assigned accession number PTA-110" ensures that the antibody has a binding domain structure and conformation common to the genus or a percentage homology to a defined sequence.

Contrary to the Examiner's assertion that a reduction to practice of the variants taught in the specification is required to fulfil the written description requirement of 35 U.S.C. § 112, first paragraph, the Federal Circuit has most recently stated that the description is deemed sufficient if it demonstrates to the skilled artisan that the applicant was in possession of the necessary common attributes of the members of the genus. *Eli Lilly*, 119 F.3d at 1568.

For the PTO's interpretation of written description support for protein claims, the Examiner is invited to review the Revised Interim Written Description Guidelines Training Materials published in the PTO web site (http://www.uspto.gov/web/menu/written.pdf), with particular reference to Example 14 at page 53, which analyzes the following product by function claim: "A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B." The PTO concludes that the disclosure does meet the requirements of 35 U.S.C. § 112, first paragraph, as providing adequate written description for the claimed invention. The reasons cited for this conclusion include (i) the novelty of SEQ ID NO:3; (ii) the conventional nature of the procedures for making variants of SEQ ID NO:3, (iii) the teaching of an assay that will identify other proteins having the claimed catalytic activity; and (iv) the recitation that all variants must possess the specified catalytic activity. These factors, the PTO states, give rise to the conclusion that "the single species disclosed is representative of the genus."

The presently claimed invention meets criteria (i) through (iv) set forth by the Patent Office. Each of the S2C6 heavy chain CDRs (SEQ ID NOS:8, 9 and 10, respectively), and a variable region that provides the claimed binding specificity and function to increase CD40L binding to CD40, are novel; variants of S2C6 are easily made using standard molecular biology techniques, as described in Sections 5.6 and 5.7 of the specification at pages 24 and 28 and as is commonly known in the art; the disclosure teaches a plurality of assays that test for the specific activity of S2C6, that is, binding to CD40 and/or increasing the binding of CD40L to CD40 (see page 29, lines 3-18 and page 54, lines 6-18, respectively, of the instant specification); and the claims rejected for lack of written description, claims 1-9, 21-25, 34 and 36, as amended, all recite the functional limitation "binds to CD40" or "increases the binding of CD40 ligand to cell surface CD40 by at least 45%."

If the teaching of a single species having the above criteria is sufficiently representative of a genus, then surely Applicants' disclosure, which describes a large number of representative species of the claimed genuses, including monoclonal antibodies, humanized antibodies, chimeric antibodies, single chain antibodies, bispecific antibodies, Fab fragments, $F(ab')_2$ fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above (page 24, lines 28-32); antibody derivatives with substitutions, insertions or deletions relative to S2C6 (page 29, lines 24-27); fragments of S2C6 (page 30, lines 21-26); proteins with homology

to S2C6 or that are encoded by a nucleic acid sequence that is capable of hybridizing under conditions of high stringency to S2C6-encoding sequences (page 20, lines 27-36); S2C6 fragments or derivatives that are differentially modified during or after translation (*e.g.*, by glycosylation) (page 32, line 32 to page 33, line 3); chimeric or fusion proteins comprising S2C6 or a fragment or derivative thereof and a second protein, such as a biological response modifier or a toxin (page 33, line 29 to page 34, line 16) or a chemotherapeutic agent (page 35, lines 20-27), is more than representative of the claimed genuses.

In view of the foregoing, Applicants respectfully maintain that the rejection of claims 1-9, 21-25, 34 and 36 under 35 U.S.C. § 112, first paragraph, for lack of written description is improper and request that the rejection be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN

The Examiner has rejected claims 1, 2, 3, 7, 8, and 34 under 35 U.S.C. § 102(b) as being anticipated by either Kwekkeboom *et al.*, 1993, Immunology 79:439-44 ("Kwekkeboom") or Bjorck *et al.*, 1994, Immunology 83:430-37 ("Bjorck"), under the doctrine of inherent anticipation. Similarly, the Examiner has rejected claims 1, 2, 3, 7, 8, and 38 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,874,082 to de Boer ("de Boer"), under the doctrine of inherent anticipation. The Examiner's basis for the rejections is that these references disclose anti-CD40 antibodies that are not S2C6, which therefore must comprise one or more substitutions or insertions relative to S2C6. The Examiner alleged that the burden had been shifted to the Applicants to prove that the claims do not read on the antibodies disclosed in Kwekkeboom, Bjorck and de Boer. For the reasons discussed below, Applicants respectfully traverse this rejection.

THE LEGAL STANDARD

The Examiner cites *In re Best*, 562 F, 2d 1252 (CCPA 1977) and *Ex parte Gray*, 10 U.S.P.Q. 2d 1922 (PTO Bd. Pat. App. & Int. 1989) as the legal grounds for shifting the burden to the Applicants to prove that the anti-CD40 antibodies taught in each of the foregoing references are not within the scope of the claimed invention. Both cases cited by the Examiner are distinguishable from the present situation.

In *Best*, the Applicants claimed a method for preparing zeolitic molecular sieve catalyst compositions comprising a number of steps, and the compositions themselves. One of the prior art references, Hansford, expressly disclosed essentially the same method as that claimed by Applicants, but was silent regarding a cooling rate

limitation (of the zeolite) recited by Applicants. *Best*, 562 F.2d at 1253-54. Hansford, however, did disclose removal of the zeolite from a heat source. The PTO concluded that cooling down was an inherent feature of the Hansford process, resulting from removal of the zeolite from the heat source, and shifted the vurden on the Applicants to prove otherwise. In its analysis, the Court of Customs and Patent Appeals ("CCPA") employed a two prong test to determine whether the prior art inherently anticipated the claimed invention: (1) whether the PTO reasonably asserted inherency, and, if so, (2) whether the Applicants rebutted the assertion. *Id.* at 1254. With respect to what is a reasonable assertion of inherency, the CCPA stated that "[w]here, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product." *Id.* at 1255.

In *Gray*, Applicants cloned the gene for human β-nerve growth factor. The claims were directed to, *inter alia*, a purified β-nerve growth factor identified by the sequence encoded by the cloned gene. The prior art cited by the Examiner taught purified forms of human β-nerve growth factor. The Board of Patent Appeals and Interferences ("the Board") alleged that the claimed and prior art products were the same, and differed only with respect to the method of making the products (which in the prior art entailed purification from cells, as opposed to Applicants' method of purification from a recombinant expression system). *Gray* at 1924. However, the Board noted that "the dispositive issue before us is whether the claimed factor exhibits any unexpected properties compared with that described by the cited [art]." *Id.*

Thus, both *Best* and *Gray* conclude that an assertion of inherency by the PTO is reasonable where the prior art product is identical or substantially identical to the claimed product. What reasonably follows from *Best* and *Gray* is that, where a claimed product is shown to possess distinct properties from the prior art product, the assertion of inherency is unreasonable and/or has been rebutted.

THE CITED REFERENCES

In view of the foregoing legal standard, Applicants have amended claim 1 to recite an S2C6 heavy chain CDR (SEQ ID NOS:8, 9 or 10) and claim 8 to recite at least 95% identity to the S2C6 heavy chain variable region (SEQ ID NO:7), respectively, since the heavy chain CDRs (which are included within the variable region) are the main determinants of epitope specificity and thus functionality. As will be discussed below, the

prior art anti-CD40 antibodies display different functional properties from S2C6, and thus do not inherently anticipate the claimed invention.

de Boer

de Boer describes a class of antibodies including the monoclonal antibody 5D12, which prevents the growth and differentiation of B cells and blocks the CD40-CD40L interactions. In Example 2 at column 17, de Boer describes experiments comparing the effect of the anti-CD40 monoclonal antibodies 5D12, 3A8, 3C6 and S2C6 on tonsillar B cells in the presence of immobilized IgM and interleukin-2 (IL-2). The data of the experiments described in Example 2 are shown Figure 5. S2C6, but not 5D12, 3A8 or 3C6 was able to stimulate B cell proliferation in either the presence of immobilized IgM (Figure 5A) or IgM plus IL-2 (Figure 5B). Moreover, antibodies 5D12, 3A8 or 3C6 in fact inhibited S2C6's activity on B cells in the presence of IgM (see Example 4 at column 18 and Figure 6).

Clearly, then, the activities of 5D12, 3A8 or 3C6 are distinct from those of S2C6 and thus 5D12, 3A8 or 3C6 cannot be said to inherently possess the same characteristics as claimed subject matter having at least a heavy chain CDR of S2C6.

5D12 Sequence Analysis

An analysis of the sequence of 5D12 confirms Applicants' remarks made above. de Boer discloses the sequence of murine 5D12 and that of a humanized counterpart. A sequence alignment of the heavy and light chain variable regions of 5D12 and humanized 5D12 with their S2C6 counterparts is attached hereto as Exhibit Q.

With respect to claim 1 as amended, which is directed to a "molecule comprising SEQ ID NO:8, SEQ ID NO:9, or SEQ ID NO:10" that "binds CD40" and "comprises one or more substitutions or insertions in primary amino acid sequence relative to" S2C6, neither the murine nor the humanized 5D12 antibody anticipates the claim, because neither comprises SEQ ID NO:8, SEQ ID NO:9, or SEQ ID NO:10 (which corresponds to S2C6 heavy chain CDR1, CDR2, and CDR3, respectively). As Exhibit Q shows, the corresponding CDRs of 5D12 (which are the same in the murine and humanized antibodies) have only 20, 29.4 and 0% sequence identity to SEQ ID NOS:8, 9 and 10, respectively. Thus, antibody 5D12 does not anticipate claim 1 and claims 2, 3, 7 and 34 dependent thereon.

Further, the disclosed sequence of 5D12 confirms Applicants' remarks above for claim 8, which is directed to a purified protein comprising, *inter alia*, an amino acid sequence having at least 95% identity to SEQ ID NO:7, which is the sequence of the variable region of the S2C6 heavy chain. As clearly indicated in Exhibit Q, the corresponding heavy chain regions of murine and humanized 5D12 have only 42.1% and 44.7% sequence identity to SEQ ID NO:7, respectively.

Kwekkeboom

Kweekeboom is co-authored by de Boer and is an earlier paper that discloses the same antibodies as disclosed by de Boer, 5D12, 3A8 and 3C6. Figure 1(a) in Kwekkeboom corresponds to Figure 5A in de Boer and shows that S2C6, but not 5D12, 3A8 or 3C6, stimulates the proliferation of tonsillar B cells in the presence of immobilized IgM. Figure 1(b) in Kwekkeboom corresponds to Figure 5B in de Boer and shows that S2C6, but not 5D12, 3A8 or 3C6, stimulates the proliferation of tonsillar B cells in the presence of immobilized IgM and IL-2. Figure 2 of Kwekkeboom shows that antibodies 5D12, 3A8 or 3C6 inhibit S2C6-induced proliferation of B cells (corresponding to Figure 6 of de Boer).

Thus, like de Boer, Kwekkenboom teaches that the activities of 5D12, 3A8 or 3C6 are distinct from those of S2C6 and thus 5D12, 3A8 or 3C6 cannot be said to inherently fall within the scope of rejected claims 1, 2, 3, 7, 8 and 34.

Bjorck

Bjorck discloses two anti-CD40 monoclonal antibodies 17:40 and mAb89 other than S2C6, but clearly demonstrates that the two antibodies have functional characteristics that distinguish them from S2C6 and thus the claimed subject matter of claims 1, 2, 3, 7, 8 and 34.

With respect to 17:40, Bjorck teaches that unlike S2C6, 1740 does not react with B95-8, a marmoset B cell line, "indicating the recognition of a more species-restricted epitope" by 17:40 (page 431, right column). Another distinguishing feature of S2C6 over 17:40 is the former but not latter's costimulatory activity with CD40L (referred to by Bjorck by its alternative nomenclature of gp39) on B cells in the presence of interleukin-4 ("IL-4") (page 433, left and right columns and table 2). 17:40 and S2C6 also differ in their ability to inhibit the binding of CD40L to immobilized CD40 -- while 17:40 inhibited CD40L binding to immobilized CD40 by over 98%, even at the highest concentrations tested, S2C6

only partially blocked CD40L binding to CD40 (by less than 58%) (see page 434, right column and table 4).

Comparing mAb89 with S2C6 also reveals a number of important differences. In a B cell proliferation assay, for example, whereas mAb89 only had slightly synergistic or an additive effect with 17:40 on B cell proliferation, S2C6 and 17:40 displayed a highly synergistic effect (page 433, left column and Table 2). Also, while S2C6 enhanced CD40L-stimulated proliferation of B cells in the presence of IL-4, mAb89 had the opposite effect of inhibiting CD40-induced proliferation of B cells in the presence of IL-4 (page 433, right column and Table 2). Conversely, while mAb89 stimulated IgE synthesis in B cells in the presence of IL-4, S2C6 had little effect on IgE synthesis (page 433, right column and page 434 at Table 3). Further, while mAb89, like 17:40 inhibited CD40L binding to immobilized CD40 by over 97%, even at the highest concentrations tested, S2C6 only partially blocked CD40L binding to CD40 (by less than 58%) (see page 434, right column and table 4).

Because of these data and cross-competition assays (the results of which are noted in Table 4 on page 434), Bjorck concludes (in Figure 2 on page 434) that 17:40 has non-overlapping epitope specificity with S2C6 and mAB89 has partially overlapping yet distinct epitope specificity from that of S2C6.

In view of the foregoing, Applicants assert that the prior art products, *i.e.*, the antibodies disclosed in de Boer, Kwekkeboom and Bjorck are neither identical nor substantially identical to, and therefore do not anticipate, the presently claimed invention of claims 1, 2, 3, 7, 8 and 34. Applicants thus request that the rejection of claims 1, 2, 3, 7, 8 and 34 under 35 U.S.C. § 102 be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 1, 2, 3, 4,7, 8, and 34 are rejected under 35 U.S.C. § 103(a), allegedly as being unpatentable over Kwekkeboom or Bjorck in light of Uckun *et al.*, 1990, Blood 76:2449-2456 ("Uckun"). The basis for this rejection is that Kwekkeboom or Bjorck apparently

> teach a purified antibody, not of the IgG1 isotype, said antibody immunospecifically binds CD40 antigen on B cells, said antibody comprising SEQ ID NO: 2, 3, 4, 7, 8, 9, or 10, or SEQ ID NO: 1 and 7, in addition to one or more substitutions or insertions in the primary amino acid sequence relative to native monoclonal antibody S2C6

(emphasis added), and "Uckun teaches anti CD40 antibodies fused to non-immunoglobulin proteins." Therefore, the Examiner concludes, it would have been prima facie obvious for one of skill in the art to fuse the antibodies of Kwekkeboom or Bjorck with a non-immunoglobulin protein.

The rejection of claims 1, 2, 3, 4, 7, 8, and 34 over Kwekkeboom or Bjorck, which is based upon inherent anticipation by Kwekkeboom or Bjorck, is improperly raised under 35 U.S.C. § 103 and must be reversed, since § 102 is the statutory section under which inherent anticipation is properly raised. As stated by the Court of Appeals for the Federal Circuit:

> The district court did not, however, nor does Garlock, apply the Graham criteria, supra, to the '390 claims, apparently assuming that the claimed products, having been found inherent in the processes of Sumitomo and Smith, would have been obvious in view of those references. If so, that was error. Inherency and obviousness are distinct concepts. In re Spormann, 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966).

W.L. Gore & Assocs., Inc. v. Garlock, Inc., 721 F.2d 1540, 1554, 220 U.S.P.Q. 303, 314 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Nevertheless, without prejudice to Applicants' position that the rejection is improperly raised, the argument in the preceding section of this response clearly showed that were the rejection as under § 102 is erroneous. Specifically, as Applicants have discussed extensively, the antibodies of Kwekkeboom and Bjorck are substantially different in function from S2C6, and therefore it is not reasonable to conclude that the antibodies fall within the scope of the presently claimed invention (as amended), because it is unreasonable to conclude that the Kwekkeboom and Bjork antibodies comprise any of the CDRs or variable region of the S2C6 heavy chain, despite the Examiner's assertion to the contrary.

Nevertheless, although not apparent from the Office Action, assuming *arguendo* and to the extent the Examiner intended to base the rejection under § 103 on an assertion that Kwekkeboom or Bjorck suggest the claimed invention, the rejection cannot stand. This is discussed below.

To establish a *prima facie* case of obviousness, the teachings of the prior art must provide one of ordinary skill in the art with some suggestion or motivation to make the claimed composition. *In re Rijckaert*, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993). For a claimed invention to be deemed obvious in view of a prior art disclosure, the prior art disclosure must, firstly, give rise to a *suggestion of or motivation* for the claimed subject matter. Assuming such a suggestion or motivation is found, and the invention is thus arguably "obvious to try" to achieve, only then does one reaches the question of whether one of ordinary skill in the art would have had a reasonable expectation of success in achieving it. *See e.g.*, *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). However, there is nothing in Kwekkeboom or Bjorck, individually or together, that suggests or motivates the claimed invention. Thus, not even the threshold inquiry of the test for determining whether a claimed invention is obvious is met.

Uckun does not remedy the deficiencies of Kwekkeboom or Bjorck. For a more complete analysis, a copy of the full Uckun reference is attached hereto as Exhibit R (since only an abstract was provided with the Office Action dated October 18, 2000). First, Applicants note that the anti-CD40 antibody employed in Uckun's assays is G28-5, which Applicants clearly distinguish from S2C6. In particular, after comparing the effect of S2C6 on CD40L binding to CD40, Applicants state at page 54, lines 24-29 of the instant specification that "[t]hese data indicate that S2C6 differs surprisingly from G28-5... in its ability to increase CD40L/CD40 interaction."

Uckun does not provide a hint or suggestion of anti-CD40 molecules comprising SEQ ID NO:7, 8, 9 or 10 and that contain sequence substitutions or insertions relative to native S2C6, let alone a hint or suggestion of anti-CD40 molecules comprising SEQ ID NO:7, 8, 9 or 10 that further comprise a non-immunoglobulin fusion partner. Therefore, Applicants respectfully submit that the rejection under 35 U.S.C. § 103 (a) of

claims 1, 2, 3, 4, 7, 8, and 34 in view Kwekkeboom or Bjorck, further in view of Uckun, has been obviated and should be withdrawn.

Claims 2, 3, 4, 5, 7, 8, and 34 are rejected under 35 U.S.C. § 103(a), allegedly as being unpatentable over Kwekkeboom or Bjork in light of Uckun, further in view of U.S. Patent No. 5, 597,569 to Siegall ("Siegall"). According to the Examiner, Siegall teaches "bryodin fused to a monoclonal antibody that binds to a tumor associated cell surface antigen that is capable of internalization."[3] However, Siegall does not remedy the deficiencies of Kwekkeboom, Bjork and/or Uckun. Specifically, Siegall does not provide a hint or suggestion of anti-CD40 molecules comprising SEQ ID NO:7, 8, 9 or 10 and that contain sequence substitutions or insertions relative to native S2C6, nor does Siegall provide a hint or suggestion of anti-CD40 molecules comprising SEQ ID NO:7, 8, 9 or 10 that further comprise bryodin. Thus, Applicants respectfully assert that the rejection of claims 2, 3, 4, 5, 7, 8, and 34 over Kwekkeboom or Bjork in light of Uckun, further in view Siegall, is in error and respectfully request that it be withdrawn.

Claims 1, 2, 3, 6, 7, 8 and 34 are rejected under 35 U.S.C. § 103(a), allegedly as being unpatentable over de Boer. de Boer teaches a humanized form of the murine anti-CD40 antibody 5D12, and further suggests that "any of the anti-CD40 monoclonal antibodies of this present invention are capable of being humanized using...techniques as applied to monoclonal antibody 5D12." The Examiner concludes that because de Boer compared the activity of 5D12 with S2C6, it would have been *prima facie* obvious to one of ordinary skill in the art to make humanized forms of S2C6. Applicants believe that this conclusion is erroneous for the reasons discussed below.

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[3]Applicants point out to the Examiner that Siegall teaches bryodin 2-antibody fusions, whereas claim 5 recites "BD1", which the specification at page 6, line 4 teaches is bryodin 1.

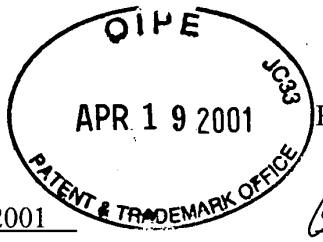
Regarding the de Boer statement at column 20, lines 41-45 that "any of the anti-CD40 monoclonal antibodies of this present invention are capable of being humanized using...techniques as applied to monoclonal antibody 5D12," this statement is directed not to S2C6, but to the antibodies, *e.g.*, 5D12, 3A8 and 3C6, which as stated in the Summary of the Invention at column 3, lines 1-17, more particularly at lines 14-17 are "capable of binding to a human CD40 antigen located on the surface of a human B cell, wherein the binding of the antibody or [an antigen binding fragment thereof] to the CD40 antigen prevents the growth or differentiation of the B cell." (Emphasis added). Thus, de Boer does not suggest the humanization of S2C6.

Further, there is no motivation in the prior art, including de Boer, to clone and humanize or otherwise genetically engineer an antibody such as S2C6 that stimulates B cell proliferation. Not until Applicants' discovery of S2C6's surprising anti-tumor activity and ability to increase the binding of CD40L to CD40 was there any appreciation in the art that S2C6 could be used to inhibit cancer growth, and therefore the motivation for humanization of S2C6 did not exist until the present invention was made.

Further, even assuming, *arguendo*, that there was motivation in the art to make humanized S2C6, the second part of the test for determining whether a claimed invention is obvious, that is, a reasonable expectation of success, could not have been met without Applicants' teachings of the S2C6 variable chain sequences. One could not have made a humanized S2C6 until the actual molecular sequences of the CDRs (SEQ ID NOS:3, 4, 5, 8, 9 and 10) were known and such were not known in the prior art. Accordingly, Applicants respectfully assert that the rejection of claims 1, 2, 3, 6, 7, 8 and 34 under 35 U.S.C. § 103(a) over de Boer are improper and should be withdrawn.

CONCLUSION

Applicants respectfully request that the above-made amendments and remarks be entered and made of record in the file history of the present application. The Examiner is invited to contact the undersigned with any questions concerning the foregoing.



Respectfully submitted,

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32,605
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